PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 04 OT 16E	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/EP2004/011667	International filing date *(day/month/year)* 14.10.2004	Priority date *(day/month/year)* 17.10.2003
International Patent Classification (IPC) or national classification and IPC C07D405/14, A61K31/495		
Applicant ITALFARMACO S.P.A.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 3 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☒	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
06.07.2005	07.11.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Samsam Bakhtiary, M Telephone No. +49 89 2399-8556

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/011667

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-18 as originally filed

   Claims, Numbers

   1-11 as amended (together with any statement) under Art. 19 PCT

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-11
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-11
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-11
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:

   D1: EP-A-0 958 289 (JANSSEN PHARMACEUTICA NV) 24 November 1999 (1999-11-24)
   D2: EP-A-0 237 963 (HOECHST) 12 march 1987
   D3: WO 98/00113 A (SCHERING CORP) 8 January 1998 (1998-01-08)
   D4: WO 01/74808 A (AVENTIS PHARMA SA ; BENEDETTI YANNICK (FR); WESTON JOHN BERNARD (FR);) 11 October 2001 (2001-10-11)
   D5: WO 99/58529 A (BACKX LEO JACOBUS JOZEF ; VEKEN LOUIS JOZEF ELISABETH V (BE); MEERPOEL) 18 November 1999 (1999-11-18)
   D6: WO 95/17407 A (GIRIJAVALLABHAN VIYYOOR M ; BENNETT FRANK (US); SCHERING CORP (US); WA) 29 June 1995 (1995-06-29)

2. Novelty

   None of the cited documents in the search report disclose any specific compounds that could affect novelty of the claimed subject matter of this application.
   The claimed subject matter of this application can be considered as novel.

3. Inventive step

   Document D1, which is considered to represent the most relevant state of the art, discloses (cf. claim 1) a fungicidal derivative from which the subject-matter of claim 1 differs in that the one substituent on the dioxalan group is an aromatic heterocycle group (eg. pyridine) instead of a phenyl.

   The problem to be solved by the present invention may therefore be regarded as to provide novel antifungicide compounds.

The solution proposed in claim 1 and pending claims 2-11 of the present application can be considered as involving an inventive step (Article 33(3) PCT) for the following reasons.

Claim 1 and 3 of this application has been amended. The amendment concerns the removal of the possibility of having sulfur heterocycle for the group Het.
The combination of D1 with D2 becomes moot.

The Applicant provided comparative tests showing that the claimed compounds have similar or improved fungicidal activities than Itraconazole (example of D1).
This was not foreseeable for the skilled man.

Re Item VII
Certain defects in the international application

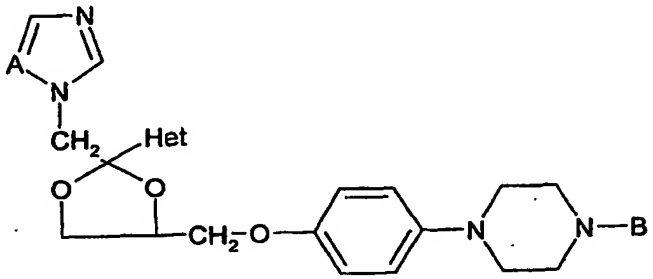
Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1 and D2 is not mentioned in the description, nor are these documents identified therein.

Re Item VIII
Certain observations on the international application

The term "residue" used in claim 1 (defining B and R1) is vague and unclear and leaves the reader in doubt as to the meaning of the technical features to which it refers, thereby rendering the definition of the subject-matter of said claims unclear, Article 6 PCT.

CLAIMS

1. A compound selected from the group consisting of the azole derivatives having the general formula

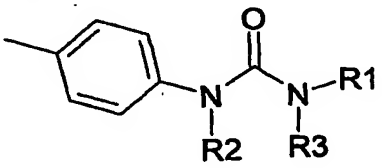


including the salts thereof with pharmaceutically acceptable acids, the N-oxide forms thereof and the stereochemical isomers thereof, where:

A is N or CH;

Het is an aromatic heterocyclic radical containing one or more O or N atoms, optionally substituted with one or more 5- or 6-membered aromatic rings;

B is an alkanoic residue containing from 1 to 6 carbon atoms or is a residue of the formula

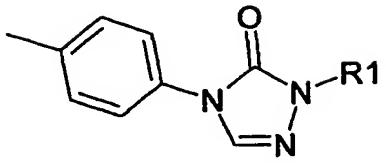


where:

R1 is hydrogen or a linear or branched alkyl residue containing from 1 to 6 carbon atoms and optionally substituted in one or more positions by hydroxyl groups;

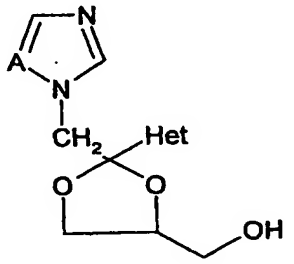
R2 and R3, taken separately, are hydrogen or an alkyl with 1-4 carbon atoms or, taken together, are a divalent radical of the formula -CH=N-, -N=CH-, -CH=CH-, $-CH_2-CH_2-$.

2. A compound according to claim 1 in which A) is a nitrogen atom.
3. A compound according to any one of the preceding claims in which Het is selected from among: pyridine, pyridazine, pyrazine, pyrimidine, oxazole, pyrrole, pyrazole, imidazole, triazole and any corresponding fusion derivatives having two or more rings or with one or more benzene rings.
4. A compound according to any one of the preceding claims in which B) is formyl, acetyl or propanoyl.
5. A compound according to any one of the preceding claims in which B has the formula:



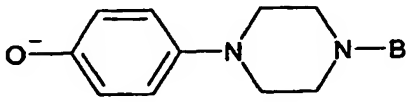
where R1 is hydrogen or a linear or branched alkyl residue containing from 1 to 6 carbon atoms and optionally substituted in one or more positions by hydroxyl groups.

6. A compound selected from the group consisting of cis-4-{4-[4-{4-[2-(2-pyridinyl)-2-(1H-1,2,4-triazol-1-yl-methyl)-1,3-dioxolan-4-yl-methoxy]phenyl}-1-piperazinyl]-phenyl}-2-(1-methyl)-propyl-2,4-dihydro-3H-1,2,4-triazol-3-one, the salts thereof with pharmaceutically acceptable acids and the stereochemical isomers thereof.
7. A compound according to claims 1-6 for use as a medicament.
8. Use of a compound according to claims 1-6 for the production of a pharmaceutical formulation for treating fungal and bacterial infections.
9. Use according to claim 8 for treating infections by *Candida albicans, Candida glabrata, Candida parapsilosis, Aspergillus fumigatus.*
10. A pharmaceutical composition containing a compound according to claims 1-6, alone or in combination with at least one other active ingredient, together with one or more pharmaceutically acceptable excipients and/or auxiliary substances.
11. A process for the production of a compound according to claims 1-6 in which a compound of the formula III



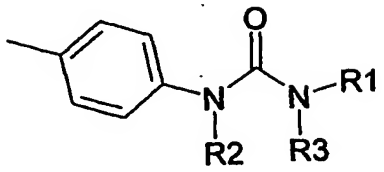
Formula (III)

where: A is N or CH and Het is an aromatic heterocyclic radical containing one or more O or N atoms, optionally substituted with one or more 5- or 6-membered aromatic rings;
is reacted with a compound of the formula



Formula (IV)

where: B is an alkanoic residue containing from 1 to 6 carbon atoms or is a residue of the formula



where: R1 is hydrogen or a linear or branched alkyl residue containing from 1 to 6 carbon atoms and optionally substituted in one or more positions by hydroxyl groups; R2 and R3, taken separately, are hydrogen or an alkyl with 1-4 carbon atoms or, taken together, are a divalent radical of the formula -CH=N-, -N=CH-, -CH=CH-, $-CH_2-CH_2-$.